

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 6/00		A1	(11) International Publication Number: WO 00/28946 (43) International Publication Date: 25 May 2000 (25.05.00)																																																																
(21) International Application Number: PCT/US99/05072 (22) International Filing Date: 9 March 1999 (09.03.99)		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).																																																																	
(30) Priority Data: 09/190,717 12 November 1998 (12.11.98) US		Published <i>With international search report.</i>																																																																	
(71) Applicant: MINNESOTA MINING AND MANUFACTURING COMPANY [US/US]; 3M Center, P.O. Box 33427, St. Paul, MN 55133-3427 (US).																																																																			
(72) Inventors: TROM, Matt, C.; P.O. Box 33427, Saint Paul, MN 55133-3427 (US). OXMAN, Joel, D.; P.O. Box 33427, Saint Paul, MN 55133-3427 (US).																																																																			
(74) Agents: BJORKMAN, Dale, A. et al.; Minnesota Mining and Manufacturing Company, Office of Intellectual Property Counsel, P.O. Box 33427, Saint Paul, MN 55133-3427 (US).																																																																			
(54) Title: DENTAL ETCHING COMPOSITION																																																																			
<p>The graph plots the logarithm of shear modulus (log Η*) in poise against temperature in degrees Celsius (°C). The y-axis ranges from 0 to 6, and the x-axis ranges from 15 to 45. Seven data series are shown, each with a different symbol and line style. Curves 1, 2, 3, 4, 5, and 6 show a sharp increase in log Η* starting around 25°C, reaching a plateau between 4.5 and 5.5 poise. Curve 7 shows a gradual increase from 15°C to 45°C, reaching approximately 1.5 poise at 45°C.</p> <table border="1"><caption>Estimated data points from the graph</caption><thead><tr><th>Temperature (°C)</th><th>Curve 1</th><th>Curve 2</th><th>Curve 3</th><th>Curve 4</th><th>Curve 5</th><th>Curve 6</th><th>Curve 7</th></tr></thead><tbody><tr><td>15</td><td>4.5</td><td>2.5</td><td>2.5</td><td>2.5</td><td>1.5</td><td>2.0</td><td>1.0</td></tr><tr><td>20</td><td>4.5</td><td>2.5</td><td>2.5</td><td>2.5</td><td>1.5</td><td>2.0</td><td>1.0</td></tr><tr><td>25</td><td>4.5</td><td>3.0</td><td>3.0</td><td>3.0</td><td>2.0</td><td>2.5</td><td>1.0</td></tr><tr><td>30</td><td>4.5</td><td>4.5</td><td>4.5</td><td>4.5</td><td>3.5</td><td>4.0</td><td>1.5</td></tr><tr><td>35</td><td>4.5</td><td>4.5</td><td>4.5</td><td>4.5</td><td>4.5</td><td>4.5</td><td>2.0</td></tr><tr><td>40</td><td>4.5</td><td>4.5</td><td>4.5</td><td>4.5</td><td>4.5</td><td>4.5</td><td>2.0</td></tr><tr><td>45</td><td>4.5</td><td>4.5</td><td>4.5</td><td>4.5</td><td>4.5</td><td>4.5</td><td>1.5</td></tr></tbody></table>				Temperature (°C)	Curve 1	Curve 2	Curve 3	Curve 4	Curve 5	Curve 6	Curve 7	15	4.5	2.5	2.5	2.5	1.5	2.0	1.0	20	4.5	2.5	2.5	2.5	1.5	2.0	1.0	25	4.5	3.0	3.0	3.0	2.0	2.5	1.0	30	4.5	4.5	4.5	4.5	3.5	4.0	1.5	35	4.5	4.5	4.5	4.5	4.5	4.5	2.0	40	4.5	4.5	4.5	4.5	4.5	4.5	2.0	45	4.5	4.5	4.5	4.5	4.5	4.5	1.5
Temperature (°C)	Curve 1	Curve 2	Curve 3	Curve 4	Curve 5	Curve 6	Curve 7																																																												
15	4.5	2.5	2.5	2.5	1.5	2.0	1.0																																																												
20	4.5	2.5	2.5	2.5	1.5	2.0	1.0																																																												
25	4.5	3.0	3.0	3.0	2.0	2.5	1.0																																																												
30	4.5	4.5	4.5	4.5	3.5	4.0	1.5																																																												
35	4.5	4.5	4.5	4.5	4.5	4.5	2.0																																																												
40	4.5	4.5	4.5	4.5	4.5	4.5	2.0																																																												
45	4.5	4.5	4.5	4.5	4.5	4.5	1.5																																																												
(57) Abstract																																																																			
<p>Dental etching compositions are provided that have the capability of undergoing an increase in viscosity in response to an increase in temperature. In a preferred embodiment, the compositions also have the ability to reverse their viscosity in response to a decrease in temperature.</p>																																																																			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

DENTAL ETCHING COMPOSITION

Field of the Invention

5 This invention relates to dental compositions suitable for etching hard tissue having viscosities capable of responding to a change in temperature. The invention also relates to methods of etching hard tissues by applying the composition directly onto a target area of the substrate.

Background

10 An etchant placed on a hard tissue will dissolve the substrate in such a way as to allow for good mechanical retention of a cured adhesive or other coating which is applied subsequent to the etching treatment. In the dental art, the use of a dental etchant is generally necessary to obtain optimal bonding of a restorative or other material to dentin or enamel. To attain proper etching at the desired location on the hard tissue, it is desirable that the etchant be controllable and slow to flow away from its target site. Thus a high viscosity etchant in the oral environment 15 would be quite useful.

20 Currently available etchants are provided in seemingly extreme viscosity states. That is, there exist compositions that have very low viscosities as well as compositions that are highly thickened and therefore possess high viscosity. Those with low viscosities are difficult to control and have tendencies to flow away from the target site once it is applied. Compositions with high viscosities are difficult to extrude through a small orifice.

25 Certain etchant compositions may use thickeners such as fumed silica and polyvinyl alcohols. Problems encountered in using these thickeners include aging, which results in non-homogenous gels which make handling difficult, and shear thinning, which reduces the viscosity of a gel when extruded through an orifice and thinning at elevated temperatures. Thinning can result in a material that drips onto soft tissue causing irritation and damage to the tissue.

Summary of the Invention

5 The present invention provides a dental composition suitable for etching hard tissue comprising an acid and a thermally responsive viscosity modifier, capable of undergoing an increase in viscosity in response to an increase in temperature. These compositions also preferably have the ability to reverse their viscosity upon the lowering of temperature.

10 Compositions of the invention work very well in the oral environment where temperature is generally higher than ambient or the pre-treatment temperature of a composition. This differential in temperature thickens the composition and thus provides a thickened, semi-solid or gel-like composition in the oral environment.

15 A preferred method of use of the invention comprises applying the composition directly onto the hard tissue. Upon exposure of the composition to the oral temperature, the composition thickens to a semi-solid or gel-like state.

Brief Description of the Drawing

Fig. 1 is a graphic illustration of the viscosity versus temperature data as described in Example 1.

20 Detailed Description of the Invention

The art of etching hard tissue typically requires etching a target site or controlled areas of several teeth at one time. Current etchant liquids are easy to dispense and apply, but these tend to flow away from the target area of application. Consequently, an etch patch could be larger than desired or, more undesirably, contact with the soft tissue could occur, which can cause sensitivity or irritation. A large etch patch unnecessarily increases the risk of decalcification during treatment. Some compositions have been provided in thickened states to provide less flow and mobility; however, they are often difficult to dispense.

25

30 The present invention provides an etching composition in a low viscosity state prior to application onto hard tissue, but which also is highly viscous, thick and controllable at the target site. These compositions are easily dispensed,

5 applied, and manipulated when handled by the user, and are easily controlled upon application to the target site. Because the composition has a low viscosity initially at a pre-treatment temperature, it requires lower syringe extrusion forces to deliver the compositions to the intended site. In turn, this would allow a user the alternative of using a brush or other applicator to apply the etchant. In addition, production of low viscosity compositions may provide easier processing and greater uniformity and consistency.

10 Compositions of this invention are particularly suitable for use in the intraoral environment where a composition having a pre-treatment temperature at or lower than ambient (room temperature) is applied to a user's hard tissue that is near or at oral temperature of about 30°C to about 39°C. For certain dental applications, it is preferred that the composition be thermally reversible. In that application, the composition not only has the ability to increase its viscosity at an elevated intra-oral temperatures, but also reverses or decreases its viscosity upon a 15 decrease in temperature.

20 The capacity of the dental composition to thicken at oral temperatures is a critical feature of the invention, for it is in this property that many of the disadvantages of previous approaches are overcome. The dissipative characteristic of liquid solutions is avoided since the compositions herein experience thickening at the site of treatment. Moreover, the problems of formulation, handling, delivery and application of viscous compositions are overcome since the present 25 compositions may be free-flowing liquids prior to treatment.

25 A "semi-solid," as used herein, is a material whose physical state is between the solid and liquid state, in which pure or mixed solvent or solution is entrained within a network, and can alternatively be considered a gel. By "pure or mixed solvent and/or solution," as stated herein, it is recognized that a mixture of solvents may be absorbed by the network. Additionally, the solvent may include salts or other additives so as to form a solution, which may also be absorbed or entrained within the network.

30 "Thickening" as used herein, is where a composition undergoes a substantial increase in the viscosity of the composition. The degree of thickening is dependent on the initial viscosity of the composition.

In a preferred embodiment of the invention, the initial viscosity of the composition may be low enough such that the composition is in a liquid state. Subsequently, upon exposure to a temperature of about near or at oral temperature, the viscosity increases to result in a thickened composition. A viscosity increase in the range of about 10- to 100-fold can be experienced when the initial viscosity is such that the composition is a liquid. Thus, for example, a composition in a liquid state may have a viscosity of about 0-7000 poise. In response to an increase in temperature, the viscosity of the composition can increase to at least about 10,000 poise. Upon the lowering of the temperature, the composition preferably has the ability to reverse its viscosity and return to flow properties of a liquid.

Yet another preferred embodiment of the invention is when the initial viscosity of the composition is at a level at which the composition is in a semi-solid state at pre-treatment temperature (viscosity is at least about 5000 poise), and upon exposure to a higher treatment temperature, the composition transforms into an "ultra-thick" composition or one with a substantially higher viscosity and very low flow characteristics. For compositions having initially high viscosities, the degree of thickening is typically 2- to 5-fold.

The pre-treatment temperature is the temperature at which the composition is subjected to prior to application or treatment. The range for the pre-treatment temperature can be about 5°C to about 29°C, although there may be certain instances where the temperature may be outside this range. Having a pre-treatment temperature at about 20°C to 25°C allows the composition to be easily stored at ambient or room temperature. Alternatively, the compositions of the invention can also be advantageously stored at lower, refrigeration pre-treatment temperatures of about 5°C to about 10°C to provide improved stability and shelf life.

The treatment temperature is the temperature which the composition is exposed to during intraoral application. This can be at or near body temperature, or about 30°C to about 39°C.

In accordance with the invention, the dental composition consists of a water-miscible, physiologically compatible medium which is liquid at ambient temperature below about 30°C and experiences thickening at oral temperatures above about 30°C. It has been found that a composition having a thickening

transition temperature in the range of from about 25°C to about 40°C is useful in the practice of the present invention. Preferably, the thickening occurs in a temperature range of from about 25°C to about 39°C, and more preferably from about 30° to about 35°C.

5 Compositions of this invention are comprised of a solvent, an acid, and one or more polymeric substances that provide the desired viscosity increase at the desired elevated temperature range in the said composition. Optionally, other adjuvants may be added to the composition. Preferably, the composition of this invention should be physiologically compatible so that no adverse reaction occurs
10 if the etching composition comes in contact with human tissue or fluids.

As used herein, a "thermally responsive viscosity modifier" is one or more polymeric substances that provides the composition or polymeric system the capability of substantially changing its viscosity in response to a change in temperature. Suitable polymeric substances useful as thermally responsive
15 viscosity modifiers include polyoxyalkylene polymers, particularly the polymeric surfactants available under the tradename PLURONIC. This class of polymers is available commercially from BASF Wyandotte Corporation. Other polyoxyalkylene polymers may also be useful as a thermally-responsive composition material.

20 A preferred dental composition in accordance with this invention comprises an aqueous solution of a selected polyoxyethylene-polyoxypropylene block copolymer. A composition comprising polyoxyethylene-polyoxypropylene block copolymers in which the number of polyoxyethylene units is at least about 50% of the number of units in the total molecule, and the block copolymer having an average molecular weight of from about 1100 to about 15,500 has been found
25 to be particularly useful. It is more preferable that a composition comprises about 70% polyoxyethylene units of the total number of monomeric units in the copolymer and the copolymer has an average molecular weight of about 11,500. PLURONIC F-127 is a material that meets these criteria.

30 The PLURONIC polymers are closely related block copolymers that may be generically classified as polyoxypropylene-polyoxyethylene condensates that terminate in primary hydroxyl groups. These polymers are formed by the

condensation of propylene oxide into a propylene glycol nucleus followed by the condensation of ethylene oxide onto both ends of the polyoxypropylene base. The polyoxyethylene hydrophilic groups on the ends of the base pre-polymer are controlled in length to constitute from about 10% to about 80% by weight of the final polymer.

5 The PLURONIC polymer series of products may be represented empirically by the formula: $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_cH$ where a and c are statistically equal.

10 The concentration of the block copolymers is an important parameter and can be formulated in such a manner corresponding to the other components' concentrations. By adjusting the concentration of the copolymer to accommodate other solutes present in the vehicle, any desired liquid to semi-solid transition temperature in the critical range of above ambient temperature and below body temperature can be achieved. Thus, the principal consideration is the selection of a 15 concentration which, in conjunction with all of the constituents of the total composition, will provide a liquid to semi-solid transition temperature in the required range.

20 It has been found that a useful block copolymer concentration is from about 5% to about 40% by weight (wt. %) of the composition, particularly from about 17 wt. % to about 26 wt. % of the composition. Excellent results have been obtained 25 using aqueous solutions having from about 17 wt.% to about 29 wt. % of PLURONIC F-127. Increased polymer concentrations may be required in highly acidic systems to affect the same results as in a less acidic system so that, in optimizing the thickening or gelation characteristics for a system, the pH of the solution must be taken into account.

30 Particularly preferred polymers for the present invention are the PLURONIC F-127 and F-108. These viscosity modifiers are block copolymers of ethylene oxide and propylene oxide. Thickening tendencies of block copolymers increase as ethylene oxide content and total molecular weight increase. Thermally responsive block copolymers have been disclosed in U.S. Patent Nos. 4,474,751; 4,474,752; 5,441,732; and 5,252,318, as well as the Product Catalog, "BASF Performance Chemicals," all the teachings of which are incorporated by reference

herein. These block copolymers offer extremely low toxicity and a high degree of mildness for applications involving human contact.

5 A preferred solvent for the composition of this invention is water. The concentration of water in the composition can be in the range of from about 30 wt.% to about 90 wt. % of the composition. Preferably, water can exist in the range of about 40 wt. % to about 80 wt. % of the composition. The water used in forming the aqueous solution is preferably purified, as by distillation, filtration, ion-exchange or the like.

10 Co-solvents may be used, including anhydrous solutions comprising a polyol component such as propylene glycol or polyethylene glycol. Glycerin may also be used as a constituent of the composition.

15 Acids for use in the present invention can be inorganic or organic acids, and if organic can be monomeric, oligomeric or polymeric. If desired, a precursor to the acid such as an acid anhydride, e.g., 4-Methacryloxyethyl Trimellitate Anhydride (4-META), acid halide (including inorganic acid halides such as Lewis acids, e.g., ferric chloride, and organic acid halides), or ester can be used in place of the acid itself, e.g., to generate the desired acid in situ. Suitable acids include mineral acids, carboxylic acids, sulfonic acids, and phenols, with carboxylic acids, alkylsulfonic acids, arylsulfonic acids, and phosphonic acids being preferred.

20 The acid has a pKa in water that is less than or equal to that of phenol. Preferably, the pKa of the acid is between about -20 and about +10, more preferably between about -10 and about +5.

25 The acid can be liquid or a solid; if a solid it should be dissolved in a suitable solvent to enable the acid to wet the hard tissue. Liquid acids can also be dissolved in a suitable solvent, e.g., in order to facilitate wetting. Preferred solvents for the acid are the film former cosolvents discussed in more detail below.

30 Suitable inorganic acids include hydrobromic acid, hydrochloric acid, nitric acid, phosphoric acid, and sulfuric acid. Suitable organic acids include acetic acid, α -chloropropionic acid, 2-acrylamido-2-methylpropanesulfonic acid, acrylic acid, benzenesulfonic acid, benzoic acid, bromoacetic acid, 10-camphorquinone-sulfonic acid, 10-camphorsulfonic acid, chloroacetic acid, citraconic acid, citric acid, dibromoacetic acid, dichloroacetic acid, di-Hema ester of 1,2,4,5

benzenetetracarboxylic acid, 2,4-dinitrophenol, ethylenediaminetetraacetic acid (EDTA), the mono-, di- and trivalent salts of EDTA, formic acid, fumaric acid, 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid, maleic acid, methacrylic acid, 2-naphthalene sulfonic acid, oxalic acid, p-nitrophenol, phenol, phosphorous acid esters (such as 2,2'-bis(a-methacryloxy-b-hydroxypropoxyphenyl) propane diphosphonate (Bis-GMA diphosphonate), dibutyl phosphite, di-2-ethyl-hexyl phosphate, di-2-ethyl-hexyl phosphite, hydroxyethyl methacrylate monophosphate, glyceryl dimethacrylate phosphate, glyceryl-2-phosphate, glycerylphosphoric acid, methacryloxyethyl phosphate, pentaerythritol triacrylate monophosphate, pentaerythritol trimethacrylate monophosphate, dipentaerythritol pentaacrylate monophosphate, and dipentaerythritol pentamethacrylate monophosphate), pivalic acid, propionic acid, toluene sulfonic acid, tribromoacetic acid, trichloroacetic acid, trifluoroacetic acid, trifluoromethanesulfonic acid, and trihydroxybenzoic acid. Mixtures of such acids can be used if desired.

Other adjuvants can be added to the composition for various purposes. For example, a preferred embodiment of the invention can contain fluoride, a desirable additive in oral composition. Additives may also be included in the composition to promote the stability of the formulation. Anti-microbial agents, anti-fungal agents, and preservatives may be added to the composition to improve shelf-life. The compositions may further include other adjuvants such as medicaments, indicators, dyes, wetting agents, buffering agents, thixotropes, polyols and the like, contingent upon attainment of the desired degree of etching performance and suitability for use on the desired hard tissue. For example, a composition may contain indicators that communicates to the user the degree of etching that has been performed on the hard tissue. The compositions may further include other adjuvants such as fillers, cariostatic agents and flavorings.

In the practice of the present invention, the hard tissues which can be etched include human and animal tissues such as teeth, including the component parts which are enamel, dentin, and cementum. The invention has particular utility for etching dentin, sclerotic dentin, enamel, and cervical enamel. In a preferred method of the invention, the etchant is permitted to stand on the hard tissue for a desired

period of time, readily volatile cosolvents are removed therefrom (e.g., by air-drying) to modify the surface of the hard tissue.

Delivery of the composition of the invention may be performed in various methods. One method of delivery of the etching composition is the direct application of the composition onto the hard tissue. This may be done directly from the composition's container or dispenser such as a bottle, vial, syringe, or tube. Alternatively, it can be applied by using a brush to paint or coat the composition onto the hard tissue. The composition is kept on the hard tissue for a desired period to effectuate etching. The length of time the composition is in contact with the hard tissue would depend on the amount of etching desired.

A preferred method of use comprises first etching with the composition of the present invention, followed by an application of a dental material on the tissue such as a sealant or coating, restorative material, adhesive, cement, dental primer or film former. Yet another preferred method is first etching with the composition of the present invention, then followed by an application of a bonding agent for purposes of bonding an orthodontic appliance onto a tooth. The invention enables etching of hard tissue in order to improve the bond strength or durability of a restorative or coating applied thereto.

Hard tissue to which the etchant is applied preferably is first cleaned using conventional methods (e.g., by abrading it with a bur), rinsed (e.g., using water) and dried (e.g., using air). If desired, deep excavations in teeth can be lined with a conventional basing material, (e.g., calcium hydroxide or a glass ionomer cement).

The acid should be allowed to stand on the surface of the hard tissue long enough to provide the desired degree of etching. The standing time will depend upon the particular acid employed, the type of hard tissue and its intended use, and the time available for carrying out the etching procedure. For etching dentin and enamel, standing times less than about 5 minutes, and preferably about 5 seconds to one minute provide very effective etching, although shorter or longer times can be used if desired.

Where the compositions are thermally reversible, the composition can be readily removed from the hard tissue by cooling the material below the liquid to semi-solid transition temperature, thus reversing the thickening effect. This can be

accomplished with cool water or other physiologically compatible liquid.

Alternatively, the concentrations of the components in the composition may be adjusted and diluted by adding water or other liquid solution. By adjusting the concentrations of the components, the transition temperature is correspondingly adjusted, and thus provides the user the ability to remove the composition even with warm solutions. Water or other liquid solutions may be administered through a rinsing cup, squirt bottle, a liquid dispensing dental tool, or any other liquid dispensing device that can provide solution to the oral environment. Preferably, administering cool or cold water provides a significant decrease in viscosity.

10 Alternatively, the composition may be brushed, wiped, or blown off.

These and other aspects of the invention are illustrated by the following examples which should not be viewed as limiting in scope. Unless otherwise indicated, all molecular weights are number average molecular weights and all ratios, parts and percentages are by weight.

15

EXAMPLES

Example 1

Etching compositions were made in which the acid used was 3M Etchant Liquid manufactured by 3M Dental Products Division. Sample compositions 3 through 7 were mixed such that the compositions contained 15-30% by weight of PLURONIC F127 (BASF) in 3M Etchant Liquid (3M Co., St. Paul, MN).

20

Complex viscosity versus temperature data were obtained using a controlled strain rheometer ("RDA2", Rheometrics Scientific, Piscataway, New Jersey). A parallel plate geometry was used with a plate diameter of 25 mm and a gap of approximately 1 mm. Samples were subjected to an oscillatory strain of 10% applied at a frequency of 1 rad/sec while the temperature was ramped from 15° to 45°C (3°C/ min). The resulting data is shown in Fig. 1.

The compositions 1-7 are phosphoric acid gels of the following types:

Composition

30

Comparative 1 3M Dental Etchant Gel containing fumed silica (3M Co.)

Comparative 2 Contains 15.3% PLURONIC F127 + 84.7% 3M Etchant Liquid

Comparative 3 Contains 18.4% PLURONIC F127 + 81.6% 3M Etchant Liquid

4 Contains 21.3% PLURONIC F127+ 78.7% 3M Etchant Liquid
5 Contains 24.0% PLURONIC F127+ 76% 3M Etchant Liquid
6 Contains 26.5% PLURONIC F127+ 73.5% 3M Etchant Liquid
7 Contains 28.8% PLURONIC F127+ 71.2% 3M Etchant Liquid

5

Fig. 1 illustrates the viscosity of each composition in response to temperature. As seen in the Figure, the liquid to gel transition temperature for the compositions containing PLURONIC, as shown by the substantial increase in viscosity in response to temperature increases, is dependent on the concentration of the 10 PLURONIC block copolymer. The silica filled etchant (Comparative Composition 1) maintained a high, consistent viscosity throughout the temperature range.

Example 2

15 Compositions 2 and 7 were further tested using a laboratory convection oven, heated to a temperature of approximately 45°C.

The concentration of PLURONIC F127 had significant impact on the initial viscosity of the acid etchant gel as well as the temperature at which the acid 20 formed an "immobile gel." An "immobile gel" indicates that the gel did not flow readily under its own weight in small volumes but was still able to be easily manipulated into new positions using hand-held dental instruments. The composition that contained 15.3% PLURONIC F127 had a low initial viscosity similar to that of 3M Etchant Liquid and did not form an immobile gel at approximately body temperature but did form an immobile gel at approximately 45°C. The composition containing 28.8% PLURONIC F127 was a thick liquid 25 when cooled in a refrigerator at approximately 5°C, but was an immobile gel at room temperature of approximately 24°C.

Example 3

30 An acid composition (gel) containing 24% PLURONIC F127 and 76% 3M Etchant Liquid was placed on a bovine tooth heated to 37°C. The gel was extruded from a syringe as a liquid but formed an immobile gel on contact with the tooth. The gel was left in place for 30 seconds, washed with cold water and dried in the

air. There was an obvious difference between the etched and unetched surfaces indicating that the acid gel was effective.

Example 4

5 An acid gel containing 19.4% PLURONIC F127, 8.1% citric acid (Aldrich, Milwaukee, WI) and 72.5% DI water was placed on a bovine tooth heated to 37°C. The gel was extruded from a bottle as a liquid but formed an immobile gel on contact with the tooth. The gel was left in place for 45 seconds, washed with cold water and air dried. There was an obvious difference between the etched and
10 unetched surfaces indicating that the acid gel was effective.

15 The citric acid and phosphoric acid gels had similar initial viscosity and gel characteristics with significantly different levels of PLURONIC F127. More PLURONIC F127 is required in highly acidic systems to affect the same results as in a less acidic system so that, in optimizing the gelation characteristics for a system, pH of the stock etchant solution must be taken into account.

We claim:

1. A dental composition suitable for etching hard tissue comprising an acid and a thermally responsive viscosity modifier wherein the composition is capable of undergoing an increase in viscosity in response to an increase in temperature from a pre-treatment temperature to a treatment temperature.
5
2. The composition of claim 1 wherein the composition is capable of reversible thermal response by undergoing a decrease in viscosity in response to a decrease in temperature.
3. The composition of claim 1 wherein the pre-treatment temperature is no more
10 than about 29°C.
4. The composition of claim 1 wherein the pre-treatment temperature is about 5°C to about 10°C.
5. The composition of claim 1 wherein the pre-treatment temperature is about
15 20°C to about 25°C.
6. The composition of claim 1 wherein the treatment temperature is no less than about 30°C.
7. The composition of claim 1 wherein the viscosity modifier a polyoxyalkylene polymer.
8. The composition of claim 1 wherein the acid has a pK_a less than or equal to
20 that of phenol.
9. The composition of claim 1 wherein the acid has a pK_a between about -10 and about +10.
10. The composition of claim 1 wherein the acid has a pK_a between about -7 and about +5.
25
11. The composition of claim 1 wherein the acid is selected from the group consisting of polyalkenoic acid, phosphoric acid, maleic acid, citric acid, and ethylenediaminetetraacetic acid and the mono-, di- and tri-valent salts of ethylenediaminetetraacetic acid.
12. The composition of claim 1 wherein the etching agent is no less than about 1% and no more than about 50% by weight of the composition, and the viscosity modifier is no less than about 5% and no more than about 40% by weight of
30 the composition.

13. The composition of claim 1 further comprising a solvent.
14. The composition of claim 13 wherein the solvent comprises water.
15. The composition of claim 13 wherein the water is no less than about 30% by weight and no more than about 90% by weight of the composition.
- 5 16. The composition of claim 1 wherein the composition has an initial viscosity of about 0 to about 7000 poise and increases to about 10,000 poise in response to the increase in temperature.
- 10 17. A method of etching hard tissue in the oral environment using a dental composition comprising an acid and a thermally responsive viscosity modifier wherein the composition is capable of undergoing an increase in viscosity in response to an increase in temperature from a pre-treatment temperature to a treatment temperature, wherein the temperature of the hard tissue has a temperature higher than the temperature of the composition prior to treatment, comprising the steps of:
 - 15 a) applying the composition onto the hard tissue, thereby initiating an increase in the viscosity of the composition,
 - b) allowing the composition to remain on the hard tissue for a sufficient time to effectuate etching.
- 20 18. The method of claim 17 further comprising a step of c) removing the composition from the hard tissue.
19. The method of claim 17 further comprising a step of c) applying a coating of adhesive to bond an orthodontic appliance to the hard tissue.
- 25 20. The method of claim 17 further comprising a step of c) applying a dental appliance selected from the group consisting of sealants, cements, adhesives, primers, film formers, and restorative materials.
21. The method of claim 18 further comprising a step of d) applying a coating of adhesive to bond an orthodontic appliance to the hard tissue.
22. The method of claim 18 further comprising a step of c) applying a dental 30 appliance selected from the group consisting of sealants, cements, adhesives, primers, film formers, and restorative materials.

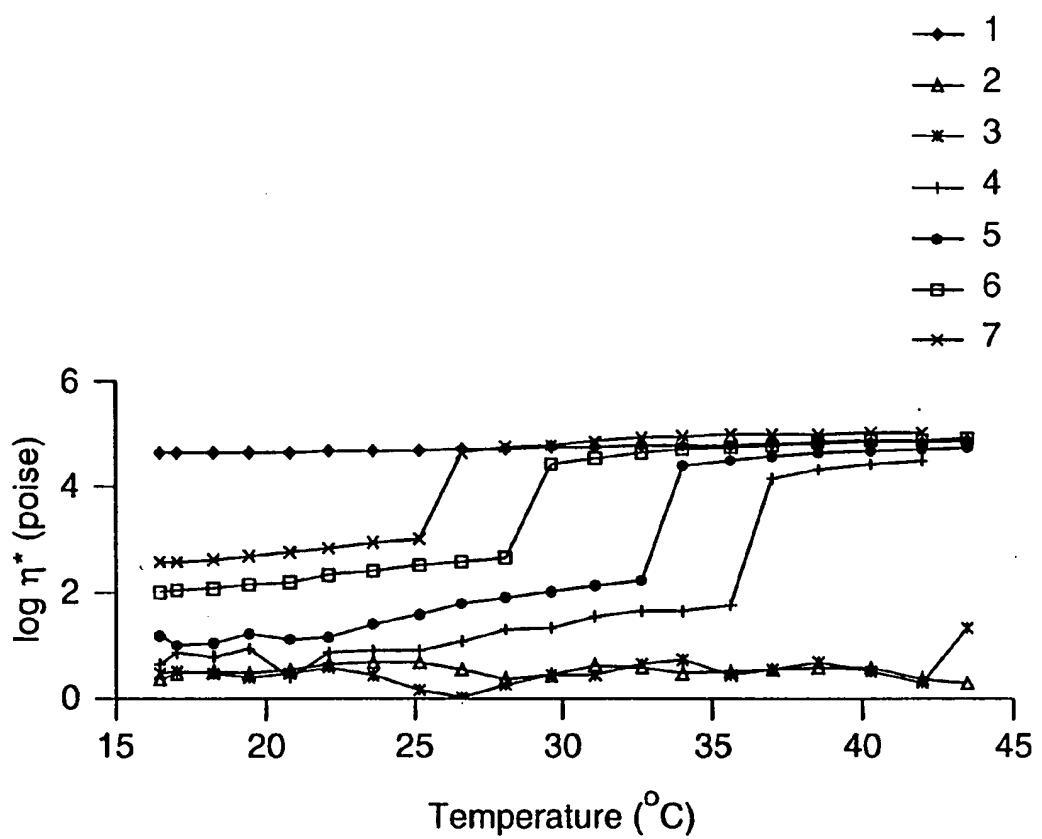


Fig.1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/05072

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K6/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category ^a	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 102 200 A (JOHNSON & JOHNSON DENTAL PROD) 7 March 1984 (1984-03-07) page 4, line 22 -page 5, line 3 example 6 --- US 4 188 373 A (KREZANOSKI JOSEPH Z) 12 February 1980 (1980-02-12) column 2, line 49 -column 3, line 36 column 3, line 61 -column 4, line 3 column 4, line 18 -column 5, line 23 column 7, line 1 - line 9 claims --- EP 0 758 544 A (SUN MEDICAL CO LTD) 19 February 1997 (1997-02-19) page 8, line 55 -page 9, line 10 --- -/-	1, 2, 7, 13-15 1, 2, 7, 13-15 17-22
A		

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

^a Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the International search report

29 September 1999

06/10/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3018

Authorized officer

Cousins-Van Steen, G

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/05072

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 008, no. 251 (C-252), 16 November 1984 (1984-11-16) & JP 59 128330 A (KURARAY KK), 24 July 1984 (1984-07-24) abstract ---	
A	EP 0 612 512 A (MINNESOTA MINING & MFG) 31 August 1994 (1994-08-31) -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members			International application No PCT/US 99/05072	
Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
EP 0102200	A 07-03-1984	AT 25332 T AU 559344 B AU 1749183 A CA 1207670 A DK 351083 A, B, ES 524657 A FI 832766 A, B, GR 78863 A HK 61487 A IE 55409 B JP 1676864 C JP 3040007 B JP 59044307 A NZ 204974 A PT 77144 A, B SG 29587 G US 4540576 A ZA 8305622 A	15-02-1987 05-03-1987 09-02-1984 15-07-1986 03-02-1984 01-12-1985 03-02-1984 02-10-1984 28-08-1987 12-09-1990 26-06-1992 17-06-1991 12-03-1984 11-10-1985 01-09-1983 17-07-1987 10-09-1985 27-03-1985	
US 4188373	A 12-02-1980	US 4100271 A AU 515420 B AU 2794977 A CA 1090252 A CH 629385 A DE 2708152 A FR 2400903 A GB 1571832 A JP 1157132 C JP 52125619 A JP 57048049 B NL 7709273 A	11-07-1978 02-04-1981 22-02-1979 25-11-1980 30-04-1982 08-09-1977 23-03-1979 23-07-1980 15-07-1983 21-10-1977 14-10-1982 27-02-1979	
EP 0758544	A 19-02-1997	CA 2183040 A JP 9110913 A US 5866632 A	11-02-1997 28-04-1997 02-02-1999	
JP 59128330	A 24-07-1984	NONE		
EP 0612512	A 31-08-1994	US 4719149 A AT 117196 T AU 586319 B AU 6872187 A BR 8700932 A CA 1308216 A CN 1016042 B DE 3750993 D DE 3750993 T DK 96287 A EG 18461 A EP 0234934 A ES 2065885 T HK 153196 A JP 2670522 B JP 62223289 A KR 9709877 B LT 1472 A, B LV 5388 A MX 165259 B	12-01-1988 15-02-1995 06-07-1989 03-09-1987 29-12-1987 29-09-1992 01-04-1992 02-03-1995 03-08-1995 29-08-1987 28-02-1993 02-09-1987 01-03-1995 16-08-1996 29-10-1997 01-10-1987 19-06-1997 26-06-1995 10-03-1994 04-11-1992	

INTERNATIONAL SEARCH REPORT

Infor. on on patent family members

International application No

PCT/US 99/05072

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0612512 A		NZ 219222 A SU 1828400 A TR 23643 A	27-10-1989 15-07-1993 28-05-1990



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 6/00		A1	(11) International Publication Number: WO 00/28946																																																
			(43) International Publication Date: 25 May 2000 (25.05.00)																																																
<p>(21) International Application Number: PCT/US99/05072</p> <p>(22) International Filing Date: 9 March 1999 (09.03.99)</p> <p>(30) Priority Data: 09/190,717 12 November 1998 (12.11.98) US</p> <p>(71) Applicant: MINNESOTA MINING AND MANUFACTURING COMPANY [US/US]; 3M Center, P.O. Box 33427, St. Paul, MN 55133-3427 (US).</p> <p>(72) Inventors: TROM, Matt, C.; P.O. Box 33427, Saint Paul, MN 55133-3427 (US). OXMAN, Joel, D.; P.O. Box 33427, Saint Paul, MN 55133-3427 (US).</p> <p>(74) Agents: BJORKMAN, Dale, A. et al.; Minnesota Mining and Manufacturing Company, Office of Intellectual Property Counsel, P.O. Box 33427, Saint Paul, MN 55133-3427 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>																																																	
<p>(54) Title: DENTAL ETCHING COMPOSITION</p> <table border="1"> <caption>Estimated data points from the graph</caption> <thead> <tr> <th>Temperature (°C)</th> <th>1</th> <th>2</th> <th>3</th> <th>4</th> <th>5</th> <th>6</th> <th>7</th> </tr> </thead> <tbody> <tr> <td>15-25</td> <td>4.5</td> <td>2.5</td> <td>2.5</td> <td>2.5</td> <td>1.5</td> <td>1.5</td> <td>0.5</td> </tr> <tr> <td>25-30</td> <td>4.5</td> <td>3.0</td> <td>3.0</td> <td>3.0</td> <td>2.0</td> <td>2.0</td> <td>0.5</td> </tr> <tr> <td>30-35</td> <td>4.5</td> <td>4.5</td> <td>4.5</td> <td>4.5</td> <td>3.5</td> <td>3.5</td> <td>1.5</td> </tr> <tr> <td>35-40</td> <td>4.5</td> <td>4.5</td> <td>4.5</td> <td>4.5</td> <td>4.5</td> <td>4.5</td> <td>1.5</td> </tr> <tr> <td>40-45</td> <td>4.5</td> <td>4.5</td> <td>4.5</td> <td>4.5</td> <td>4.5</td> <td>4.5</td> <td>0.5</td> </tr> </tbody> </table>				Temperature (°C)	1	2	3	4	5	6	7	15-25	4.5	2.5	2.5	2.5	1.5	1.5	0.5	25-30	4.5	3.0	3.0	3.0	2.0	2.0	0.5	30-35	4.5	4.5	4.5	4.5	3.5	3.5	1.5	35-40	4.5	4.5	4.5	4.5	4.5	4.5	1.5	40-45	4.5	4.5	4.5	4.5	4.5	4.5	0.5
Temperature (°C)	1	2	3	4	5	6	7																																												
15-25	4.5	2.5	2.5	2.5	1.5	1.5	0.5																																												
25-30	4.5	3.0	3.0	3.0	2.0	2.0	0.5																																												
30-35	4.5	4.5	4.5	4.5	3.5	3.5	1.5																																												
35-40	4.5	4.5	4.5	4.5	4.5	4.5	1.5																																												
40-45	4.5	4.5	4.5	4.5	4.5	4.5	0.5																																												
<p>(57) Abstract</p> <p>Dental etching compositions are provided that have the capability of undergoing an increase in viscosity in response to an increase in temperature. In a preferred embodiment, the compositions also have the ability to reverse their viscosity in response to a decrease in temperature.</p>																																																			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

DENTAL ETCHING COMPOSITION

Field of the Invention

5 This invention relates to dental compositions suitable for etching hard tissue having viscosities capable of responding to a change in temperature. The invention also relates to methods of etching hard tissues by applying the composition directly onto a target area of the substrate.

Background

10 An etchant placed on a hard tissue will dissolve the substrate in such a way as to allow for good mechanical retention of a cured adhesive or other coating which is applied subsequent to the etching treatment. In the dental art, the use of a dental etchant is generally necessary to obtain optimal bonding of a restorative or other material to dentin or enamel. To attain proper etching at the desired location on the hard tissue, it is desirable that the etchant be controllable and slow to flow away from its target site. Thus a high viscosity etchant in the oral environment would be quite useful.

15

20 Currently available etchants are provided in seemingly extreme viscosity states. That is, there exist compositions that have very low viscosities as well as compositions that are highly thickened and therefore possess high viscosity. Those with low viscosities are difficult to control and have tendencies to flow away from the target site once it is applied. Compositions with high viscosities are difficult to extrude through a small orifice.

25 Certain etchant compositions may use thickeners such as fumed silica and polyvinyl alcohols. Problems encountered in using these thickeners include aging, which results in non-homogenous gels which make handling difficult, and shear thinning, which reduces the viscosity of a gel when extruded through an orifice and thinning at elevated temperatures. Thinning can result in a material that drips onto soft tissue causing irritation and damage to the tissue.

Summary of the Invention

The present invention provides a dental composition suitable for etching hard tissue comprising an acid and a thermally responsive viscosity modifier, capable of undergoing an increase in viscosity in response to an increase in temperature. These compositions also preferably have the ability to reverse their viscosity upon the lowering of temperature.

Compositions of the invention work very well in the oral environment where temperature is generally higher than ambient or the pre-treatment temperature of a composition. This differential in temperature thickens the composition and thus provides a thickened, semi-solid or gel-like composition in the oral environment.

A preferred method of use of the invention comprises applying the composition directly onto the hard tissue. Upon exposure of the composition to the oral temperature, the composition thickens to a semi-solid or gel-like state.

Brief Description of the Drawing

Fig. 1 is a graphic illustration of the viscosity versus temperature data as described in Example 1.

The art of etching hard tissue typically requires etching a target site or controlled areas of several teeth at one time. Current etchant liquids are easy to dispense and apply, but these tend to flow away from the target area of application. Consequently, an etch patch could be larger than desired or, more undesirably, contact with the soft tissue could occur, which can cause sensitivity or irritation. A large etch patch unnecessarily increases the risk of decalcification during treatment. Some compositions have been provided in thickened states to provide less flow and mobility; however, they are often difficult to dispense.

The present invention provides an etching composition in a low viscosity state prior to application onto hard tissue, but which also is highly viscous, thick and controllable at the target site. These compositions are easily dispensed,

5 applied, and manipulated when handled by the user, and are easily controlled upon application to the target site. Because the composition has a low viscosity initially at a pre-treatment temperature, it requires lower syringe extrusion forces to deliver the compositions to the intended site. In turn, this would allow a user the alternative of using a brush or other applicator to apply the etchant. In addition, production of low viscosity compositions may provide easier processing and greater uniformity and consistency.

10 15 Compositions of this invention are particularly suitable for use in the intraoral environment where a composition having a pre-treatment temperature at or lower than ambient (room temperature) is applied to a user's hard tissue that is near or at oral temperature of about 30°C to about 39°C. For certain dental applications, it is preferred that the composition be thermally reversible. In that application, the composition not only has the ability to increase its viscosity at an elevated intra-oral temperatures, but also reverses or decreases its viscosity upon a decrease in temperature.

20 The capacity of the dental composition to thicken at oral temperatures is a critical feature of the invention, for it is in this property that many of the disadvantages of previous approaches are overcome. The dissipative characteristic of liquid solutions is avoided since the compositions herein experience thickening at the site of treatment. Moreover, the problems of formulation, handling, delivery and application of viscous compositions are overcome since the present compositions may be free-flowing liquids prior to treatment.

25 A "semi-solid," as used herein, is a material whose physical state is between the solid and liquid state, in which pure or mixed solvent or solution is entrained within a network, and can alternatively be considered a gel. By "pure or mixed solvent and/or solution," as stated herein, it is recognized that a mixture of solvents may be absorbed by the network. Additionally, the solvent may include salts or other additives so as to form a solution, which may also be absorbed or entrained within the network.

30 "Thickening" as used herein, is where a composition undergoes a substantial increase in the viscosity of the composition. The degree of thickening is dependent on the initial viscosity of the composition.

In a preferred embodiment of the invention, the initial viscosity of the composition may be low enough such that the composition is in a liquid state. Subsequently, upon exposure to a temperature of about near or at oral temperature, the viscosity increases to result in a thickened composition. A viscosity increase in the range of about 10- to 100-fold can be experienced when the initial viscosity is such that the composition is a liquid. Thus, for example, a composition in a liquid state may have a viscosity of about 0-7000 poise. In response to an increase in temperature, the viscosity of the composition can increase to at least about 10,000 poise. Upon the lowering of the temperature, the composition preferably has the ability to reverse its viscosity and return to flow properties of a liquid.

Yet another preferred embodiment of the invention is when the initial viscosity of the composition is at a level at which the composition is in a semi-solid state at pre-treatment temperature (viscosity is at least about 5000 poise), and upon exposure to a higher treatment temperature, the composition transforms into an "ultra-thick" composition or one with a substantially higher viscosity and very low flow characteristics. For compositions having initially high viscosities, the degree of thickening is typically 2- to 5-fold.

The pre-treatment temperature is the temperature at which the composition is subjected to prior to application or treatment. The range for the pre-treatment temperature can be about 5°C to about 29°C, although there may be certain instances where the temperature may be outside this range. Having a pre-treatment temperature at about 20°C to 25°C allows the composition to be easily stored at ambient or room temperature. Alternatively, the compositions of the invention can also be advantageously stored at lower, refrigeration pre-treatment temperatures of about 5°C to about 10°C to provide improved stability and shelf life.

The treatment temperature is the temperature which the composition is exposed to during intraoral application. This can be at or near body temperature, or about 30°C to about 39°C.

In accordance with the invention, the dental composition consists of a water-miscible, physiologically compatible medium which is liquid at ambient temperature below about 30°C and experiences thickening at oral temperatures above about 30°C. It has been found that a composition having a thickening

transition temperature in the range of from about 25°C to about 40°C is useful in the practice of the present invention. Preferably, the thickening occurs in a temperature range of from about 25°C to about 39°C, and more preferably from about 30° to about 35°C.

5 Compositions of this invention are comprised of a solvent, an acid, and one or more polymeric substances that provide the desired viscosity increase at the desired elevated temperature range in the said composition. Optionally, other adjuvants may be added to the composition. Preferably, the composition of this invention should be physiologically compatible so that no adverse reaction occurs 10 if the etching composition comes in contact with human tissue or fluids.

As used herein, a "thermally responsive viscosity modifier" is one or more 15 polymeric substances that provides the composition or polymeric system the capability of substantially changing its viscosity in response to a change in temperature. Suitable polymeric substances useful as thermally responsive viscosity modifiers include polyoxyalkylene polymers, particularly the polymeric surfactants available under the tradename PLURONIC. This class of polymers is available commercially from BASF Wyandotte Corporation. Other polyoxyalkylene polymers may also be useful as a thermally-responsive composition material.

20 A preferred dental composition in accordance with this invention comprises an aqueous solution of a selected polyoxyethylene-polyoxypropylene block copolymer. A composition comprising polyoxyethylene-polyoxypropylene block copolymers in which the number of polyoxyethylene units is at least about 50% of the number of units in the total molecule, and the block copolymer having an average molecular weight of from about 1100 to about 15,500 has been found 25 to be particularly useful. It is more preferable that a composition comprises about 70% polyoxyethylene units of the total number of monomeric units in the copolymer and the copolymer has an average molecular weight of about 11,500. PLURONIC F-127 is a material that meets these criteria.

30 The PLURONIC polymers are closely related block copolymers that may be generically classified as polyoxypropylene-polyoxyethylene condensates that terminate in primary hydroxyl groups. These polymers are formed by the

5

condensation of propylene oxide into a propylene glycol nucleus followed by the condensation of ethylene oxide onto both ends of the polyoxypropylene base. The polyoxyethylene hydrophilic groups on the ends of the base pre-polymer are controlled in length to constitute from about 10% to about 80% by weight of the final polymer.

10

The PLURONIC polymer series of products may be represented empirically by the formula: $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_cH$ where a and c are statistically equal.

15

The concentration of the block copolymers is an important parameter and can be formulated in such a manner corresponding to the other components' concentrations. By adjusting the concentration of the copolymer to accommodate other solutes present in the vehicle, any desired liquid to semi-solid transition temperature in the critical range of above ambient temperature and below body temperature can be achieved. Thus, the principal consideration is the selection of a concentration which, in conjunction with all of the constituents of the total composition, will provide a liquid to semi-solid transition temperature in the required range.

25

It has been found that a useful block copolymer concentration is from about 5% to about 40% by weight (wt. %) of the composition, particularly from about 17 wt. % to about 26 wt. % of the composition. Excellent results have been obtained using aqueous solutions having from about 17 wt.% to about 29 wt. % of PLURONIC F-127. Increased polymer concentrations may be required in highly acidic systems to affect the same results as in a less acidic system so that, in optimizing the thickening or gelation characteristics for a system, the pH of the solution must be taken into account.

30

Particularly preferred polymers for the present invention are the PLURONIC F-127 and F-108. These viscosity modifiers are block copolymers of ethylene oxide and propylene oxide. Thickening tendencies of block copolymers increase as ethylene oxide content and total molecular weight increase. Thermally responsive block copolymers have been disclosed in U.S. Patent Nos. 4,474,751; 4,474,752; 5,441,732; and 5,252,318, as well as the Product Catalog, "BASF Performance Chemicals," all the teachings of which are incorporated by reference

herein. These block copolymers offer extremely low toxicity and a high degree of mildness for applications involving human contact.

A preferred solvent for the composition of this invention is water. The concentration of water in the composition can be in the range of from about 5 wt.% to about 90 wt. % of the composition. Preferably, water can exist in the range of about 40 wt. % to about 80 wt. % of the composition. The water used in forming the aqueous solution is preferably purified, as by distillation, filtration, ion-exchange or the like.

10 Co-solvents may be used, including anhydrous solutions comprising a polyol component such as propylene glycol or polyethylene glycol. Glycerin may also be used as a constituent of the composition.

15 Acids for use in the present invention can be inorganic or organic acids, and if organic can be monomeric, oligomeric or polymeric. If desired, a precursor to the acid such as an acid anhydride, e.g., 4-Methacryloxyethyl Trimellitate Anhydride (4-META), acid halide (including inorganic acid halides such as Lewis acids, e.g., ferric chloride, and organic acid halides), or ester can be used in place of the acid itself, e.g., to generate the desired acid in situ. Suitable acids include mineral acids, carboxylic acids, sulfonic acids, and phenols, with carboxylic acids, alkylsulfonic acids, arylsulfonic acids, and phosphonic acids being preferred.

20 The acid has a pKa in water that is less than or equal to that of phenol. Preferably, the pKa of the acid is between about -20 and about +10, more preferably between about -10 and about +5.

25 The acid can be liquid or a solid; if a solid it should be dissolved in a suitable solvent to enable the acid to wet the hard tissue. Liquid acids can also be dissolved in a suitable solvent, e.g., in order to facilitate wetting. Preferred solvents for the acid are the film former cosolvents discussed in more detail below.

30 Suitable inorganic acids include hydrobromic acid, hydrochloric acid, nitric acid, phosphoric acid, and sulfuric acid. Suitable organic acids include acetic acid, α -chloropropionic acid, 2-acrylamido-2-methylpropanesulfonic acid, acrylic acid, benzenesulfonic acid, benzoic acid, bromoacetic acid, 10-camphorquinone-sulfonic acid, 10-camphorsulfonic acid, chloroacetic acid, citraconic acid, citric acid, dibromoacetic acid, dichloroacetic acid, di-Hema ester of 1,2,4,5

benzenetetracarboxylic acid, 2,4-dinitrophenol, ethylenediaminetetraacetic acid (EDTA), the mono-, di- and trivalent salts of EDTA, formic acid, fumaric acid, 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid, maleic acid, methacrylic acid, 2-naphthalene sulfonic acid, oxalic acid, p-nitrophenol, phenol, phosphorous acid esters (such as 2,2'-bis(a-methacryloxy-b-hydroxypropoxyphenyl) propane diphosphonate (Bis-GMA diphosphonate), dibutyl phosphite, di-2-ethyl-hexyl phosphate, di-2-ethyl-hexyl phosphite, hydroxyethyl methacrylate monophosphate, glycetyl dimethacrylate phosphate, glycetyl-2-phosphate, glycetylphosphoric acid, methacryloxyethyl phosphate, pentaerythritol triacrylate monophosphate, pentaerythritol trimethacrylate monophosphate, dipentaerythritol pentaacrylate monophosphate, and dipentaerythritol pentamethacrylate monophosphate), pivalic acid, propionic acid, toluene sulfonic acid, tribromoacetic acid, trichloroacetic acid, trifluoroacetic acid, trifluoromethanesulfonic acid, and trihydroxybenzoic acid. Mixtures of such acids can be used if desired.

Other adjuvants can be added to the composition for various purposes. For example, a preferred embodiment of the invention can contain fluoride, a desirable additive in oral composition. Additives may also be included in the composition to promote the stability of the formulation. Anti-microbial agents, anti-fungal agents, and preservatives may be added to the composition to improve shelf-life. The compositions may further include other adjuvants such as medicaments, indicators, dyes, wetting agents, buffering agents, thixotropes, polyols and the like, contingent upon attainment of the desired degree of etching performance and suitability for use on the desired hard tissue. For example, a composition may contain indicators that communicates to the user the degree of etching that has been performed on the hard tissue. The compositions may further include other adjuvants such as fillers, cariostatic agents and flavorings.

In the practice of the present invention, the hard tissues which can be etched include human and animal tissues such as teeth, including the component parts which are enamel, dentin, and cementum. The invention has particular utility for etching dentin, sclerotic dentin, enamel, and cervical enamel. In a preferred method of the invention, the etchant is permitted to stand on the hard tissue for a desired

period of time, readily volatile cosolvents are removed therefrom (e.g., by air-drying) to modify the surface of the hard tissue.

Delivery of the composition of the invention may be performed in various methods. One method of delivery of the etching composition is the direct application of the composition onto the hard tissue. This may be done directly from the composition's container or dispenser such as a bottle, vial, syringe, or tube. Alternatively, it can be applied by using a brush to paint or coat the composition onto the hard tissue. The composition is kept on the hard tissue for a desired period to effectuate etching. The length of time the composition is in contact with the hard tissue would depend on the amount of etching desired.

10 A preferred method of use comprises first etching with the composition of the present invention, followed by an application of a dental material on the tissue such as a sealant or coating, restorative material, adhesive, cement, dental primer or film former. Yet another preferred method is first etching with the composition of the present invention, then followed by an application of a bonding agent for purposes of bonding an orthodontic appliance onto a tooth. The invention enables etching of hard tissue in order to improve the bond strength or durability of a restorative or coating applied thereto.

15 Hard tissue to which the etchant is applied preferably is first cleaned using conventional methods (e.g., by abrading it with a bur), rinsed (e.g., using water) and dried (e.g., using air). If desired, deep excavations in teeth can be lined with a conventional basing material, (e.g., calcium hydroxide or a glass ionomer cement).

20 The acid should be allowed to stand on the surface of the hard tissue long enough to provide the desired degree of etching. The standing time will depend upon the particular acid employed, the type of hard tissue and its intended use, and the time available for carrying out the etching procedure. For etching dentin and enamel, standing times less than about 5 minutes, and preferably about 5 seconds to one minute provide very effective etching, although shorter or longer times can be used if desired.

25 Where the compositions are thermally reversible, the composition can be readily removed from the hard tissue by cooling the material below the liquid to semi-solid transition temperature, thus reversing the thickening effect. This can be

accomplished with cool water or other physiologically compatible liquid.

Alternatively, the concentrations of the components in the composition may be adjusted and diluted by adding water or other liquid solution. By adjusting the concentrations of the components, the transition temperature is correspondingly adjusted, and thus provides the user the ability to remove the composition even with warm solutions. Water or other liquid solutions may be administered through a rinsing cup, squirt bottle, a liquid dispensing dental tool, or any other liquid dispensing device that can provide solution to the oral environment. Preferably, administering cool or cold water provides a significant decrease in viscosity.

10 Alternatively, the composition may be brushed, wiped, or blown off.

These and other aspects of the invention are illustrated by the following examples which should not be viewed as limiting in scope. Unless otherwise indicated, all molecular weights are number average molecular weights and all ratios, parts and percentages are by weight.

15

EXAMPLES

Example 1

Etching compositions were made in which the acid used was 3M Etchant Liquid manufactured by 3M Dental Products Division. Sample compositions 3 through 7 were mixed such that the compositions contained 15-30% by weight of PLURONIC F127 (BASF) in 3M Etchant Liquid (3M Co., St. Paul, MN).

20

Complex viscosity versus temperature data were obtained using a controlled strain rheometer ("RDA2", Rheometrics Scientific, Piscataway, New Jersey). A parallel plate geometry was used with a plate diameter of 25 mm and a gap of approximately 1 mm. Samples were subjected to an oscillatory strain of 10% applied at a frequency of 1 rad/sec while the temperature was ramped from 15° to 45°C (3°C/ min). The resulting data is shown in Fig. 1.

The compositions 1-7 are phosphoric acid gels of the following types:

Composition

30

Comparative 1 3M Dental Etchant Gel containing fumed silica (3M Co.)

Comparative 2 Contains 15.3% PLURONIC F127 + 84.7% 3M Etchant Liquid

Comparative 3 Contains 18.4% PLURONIC F127 + 81.6% 3M Etchant Liquid

4 Contains 21.3% PLURONIC F127+ 78.7% 3M Etchant Liquid
5 Contains 24.0% PLURONIC F127+ 76% 3M Etchant Liquid
6 Contains 26.5% PLURONIC F127+ 73.5% 3M Etchant Liquid
7 Contains 28.8% PLURONIC F127+ 71.2% 3M Etchant Liquid

5

Fig. 1 illustrates the viscosity of each composition in response to temperature. As seen in the Figure, the liquid to gel transition temperature for the compositions containing PLURONIC, as shown by the substantial increase in viscosity in response to temperature increases, is dependent on the concentration of the 10 PLURONIC block copolymer. The silica filled etchant (Comparative Composition 1) maintained a high, consistent viscosity throughout the temperature range.

Example 2

15 Compositions 2 and 7 were further tested using a laboratory convection oven, heated to a temperature of approximately 45°C.

The concentration of PLURONIC F127 had significant impact on the initial viscosity of the acid etchant gel as well as the temperature at which the acid 20 formed an "immobile gel." An "immobile gel" indicates that the gel did not flow readily under its own weight in small volumes but was still able to be easily manipulated into new positions using hand-held dental instruments. The composition that contained 15.3% PLURONIC F127 had a low initial viscosity similar to that of 3M Etchant Liquid and did not form an immobile gel at approximately body temperature but did form an immobile gel at approximately 45°C. The composition containing 28.8% PLURONIC F127 was a thick liquid 25 when cooled in a refrigerator at approximately 5°C, but was an immobile gel at room temperature of approximately 24°C.

Example 3

30 An acid composition (gel) containing 24% PLURONIC F127 and 76% 3M Etchant Liquid was placed on a bovine tooth heated to 37°C. The gel was extruded from a syringe as a liquid but formed an immobile gel on contact with the tooth. The gel was left in place for 30 seconds, washed with cold water and dried in the

air. There was an obvious difference between the etched and unetched surfaces indicating that the acid gel was effective.

Example 4

5 An acid gel containing 19.4% PLURONIC F127, 8.1% citric acid (Aldrich, Milwaukee, WI) and 72.5% DI water was placed on a bovine tooth heated to 37°C. The gel was extruded from a bottle as a liquid but formed an immobile gel on contact with the tooth. The gel was left in place for 45 seconds, washed with cold water and air dried. There was an obvious difference between the etched and

10 unetched surfaces indicating that the acid gel was effective.

15 The citric acid and phosphoric acid gels had similar initial viscosity and gel characteristics with significantly different levels of PLURONIC F127. More PLURONIC F127 is required in highly acidic systems to affect the same results as in a less acidic system so that, in optimizing the gelation characteristics for a system, pH of the stock etchant solution must be taken into account.

We claim:

1. A dental composition suitable for etching hard tissue comprising an acid and a thermally responsive viscosity modifier wherein the composition is capable of undergoing an increase in viscosity in response to an increase in temperature from a pre-treatment temperature to a treatment temperature.
5
2. The composition of claim 1 wherein the composition is capable of reversible thermal response by undergoing a decrease in viscosity in response to a decrease in temperature.
3. The composition of claim 1 wherein the pre-treatment temperature is no more
10 than about 29°C.
4. The composition of claim 1 wherein the pre-treatment temperature is about 5°C to about 10°C.
5. The composition of claim 1 wherein the pre-treatment temperature is about 20°C to about 25°C.
15
6. The composition of claim 1 wherein the treatment temperature is no less than about 30°C.
7. The composition of claim 1 wherein the viscosity modifier a polyoxyalkylene polymer.
8. The composition of claim 1 wherein the acid has a pK_a less than or equal to
20 that of phenol.
9. The composition of claim 1 wherein the acid has a pK_a between about -10 and about +10.
25
10. The composition of claim 1 wherein the acid has a pK_a between about -7 and about +5.
11. The composition of claim 1 wherein the acid is selected from the group consisting of polyalkenoic acid, phosphoric acid, maleic acid, citric acid, and ethylenediaminetetraacetic acid and the mono-, di- and tri-valent salts of ethylenediaminetetraacetic acid.
30
12. The composition of claim 1 wherein the etching agent is no less than about 1% and no more than about 50% by weight of the composition, and the viscosity modifier is no less than about 5% and no more than about 40% by weight of the composition.

13. The composition of claim 1 further comprising a solvent.
14. The composition of claim 13 wherein the solvent comprises water.
15. The composition of claim 13 wherein the water is no less than about 30% by weight and no more than about 90% by weight of the composition.
- 5 16. The composition of claim 1 wherein the composition has an initial viscosity of about 0 to about 7000 poise and increases to about 10,000 poise in response to the increase in temperature.
- 10 17. A method of etching hard tissue in the oral environment using a dental composition comprising an acid and a thermally responsive viscosity modifier wherein the composition is capable of undergoing an increase in viscosity in response to an increase in temperature from a pre-treatment temperature to a treatment temperature, wherein the temperature of the hard tissue has a temperature higher than the temperature of the composition prior to treatment, comprising the steps of:
 - 15 a) applying the composition onto the hard tissue, thereby initiating an increase in the viscosity of the composition,
 - b) allowing the composition to remain on the hard tissue for a sufficient time to effectuate etching.
18. The method of claim 17 further comprising a step of c) removing the composition from the hard tissue.
- 20 19. The method of claim 17 further comprising a step of c) applying a coating of adhesive to bond an orthodontic appliance to the hard tissue.
- 25 20. The method of claim 17 further comprising a step of c) applying a dental appliance selected from the group consisting of sealants, cements, adhesives, primers, film formers, and restorative materials.
21. The method of claim 18 further comprising a step of d) applying a coating of adhesive to bond an orthodontic appliance to the hard tissue.
22. The method of claim 18 further comprising a step of c) applying a dental appliance selected from the group consisting of sealants, cements, adhesives, primers, film formers, and restorative materials.

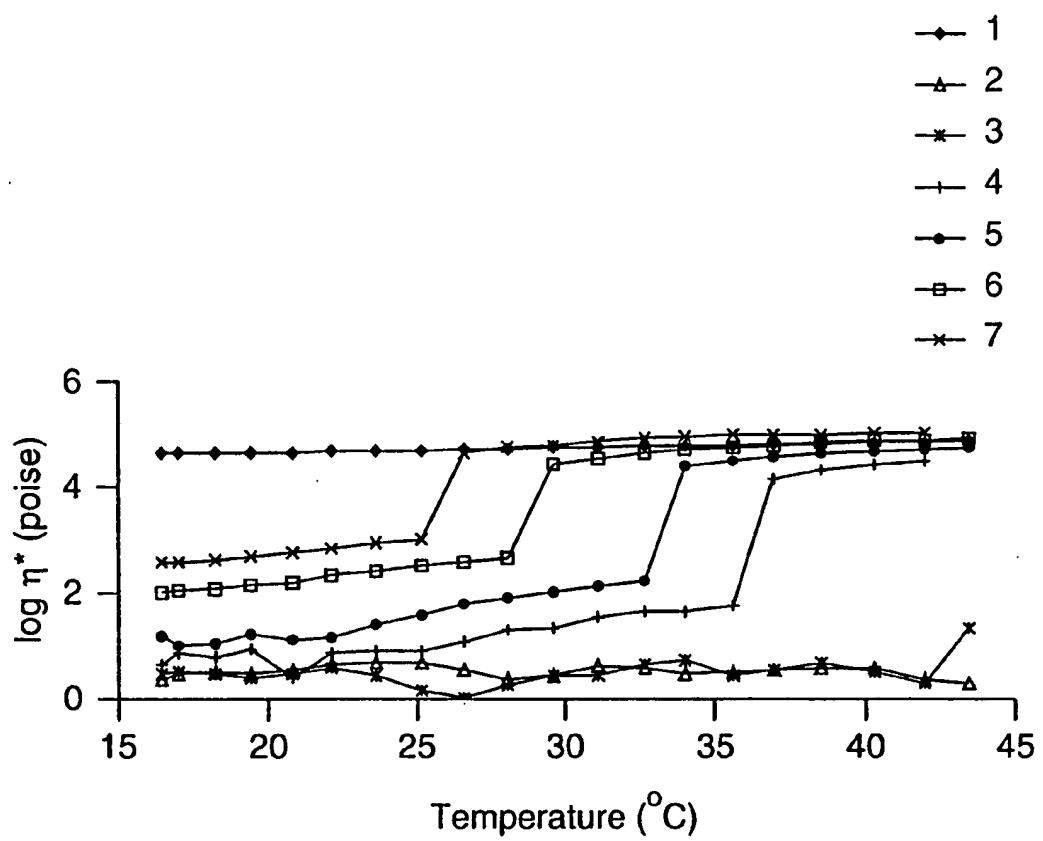


Fig.1

INTERNATIONAL SEARCH REPORT

International Application No	PCT/US 99/05072
------------------------------	-----------------

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K6/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 102 200 A (JOHNSON & JOHNSON DENTAL PROD) 7 March 1984 (1984-03-07) page 4, line 22 -page 5, line 3 example 6 ---	1,2,7, 13-15
Y	US 4 188 373 A (KREZANOSKI JOSEPH Z) 12 February 1980 (1980-02-12) column 2, line 49 -column 3, line 36 column 3, line 61 -column 4, line 3 column 4, line 18 -column 5, line 23 column 7, line 1 - line 9 claims ---	1,2,7, 13-15
A	EP 0 758 544 A (SUN MEDICAL CO LTD) 19 February 1997 (1997-02-19) page 8, line 55 -page 9, line 10 --- -/-	17-22

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

29 September 1999

06/10/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Cousins-Van Steen, G

INTERNATIONAL SEARCH REPORT

International application No	PCT/US 99/05072
------------------------------	-----------------

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 008, no. 251 (C-252), 16 November 1984 (1984-11-16) & JP 59 128330 A (KURARAY KK), 24 July 1984 (1984-07-24) abstract --- A EP 0 612 512 A (MINNESOTA MINING & MFG) 31 August 1994 (1994-08-31) -----	

INTERNATIONAL SEARCH REPORT

Info. on patent family members			International application No	
Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
EP 0102200	A 07-03-1984	AT 25332 T AU 559344 B AU 1749183 A CA 1207670 A DK 351083 A, B, ES 524657 A FI 832766 A, B, GR 78863 A HK 61487 A IE 55409 B JP 1676864 C JP 3040007 B JP 59044307 A NZ 204974 A PT 77144 A, B SG 29587 G US 4540576 A ZA 8305622 A	15-02-1987 05-03-1987 09-02-1984 15-07-1986 03-02-1984 01-12-1985 03-02-1984 02-10-1984 28-08-1987 12-09-1990 26-06-1992 17-06-1991 12-03-1984 11-10-1985 01-09-1983 17-07-1987 10-09-1985 27-03-1985	
US 4188373	A 12-02-1980	US 4100271 A AU 515420 B AU 2794977 A CA 1090252 A CH 629385 A DE 2708152 A FR 2400903 A GB 1571832 A JP 1157132 C JP 52125619 A JP 57048049 B NL 7709273 A	11-07-1978 02-04-1981 22-02-1979 25-11-1980 30-04-1982 08-09-1977 23-03-1979 23-07-1980 15-07-1983 21-10-1977 14-10-1982 27-02-1979	
EP 0758544	A 19-02-1997	CA 2183040 A JP 9110913 A US 5866632 A	11-02-1997 28-04-1997 02-02-1999	
JP 59128330	A 24-07-1984	NONE		
EP 0612512	A 31-08-1994	US 4719149 A AT 117196 T AU 586319 B AU 6872187 A BR 8700932 A CA 1308216 A CN 1016042 B DE 3750993 D DE 3750993 T DK 96287 A EG 18461 A EP 0234934 A ES 2065885 T HK 153196 A JP 2670522 B JP 62223289 A KR 9709877 B LT 1472 A, B LV 5388 A MX 165259 B	12-01-1988 15-02-1995 06-07-1989 03-09-1987 29-12-1987 29-09-1992 01-04-1992 02-03-1995 03-08-1995 29-08-1987 28-02-1993 02-09-1987 01-03-1995 16-08-1996 29-10-1997 01-10-1987 19-06-1997 26-06-1995 10-03-1994 04-11-1992	

INTERNATIONAL SEARCH REPORT

Infor. .on on patent family members

International application No

PCT/US 99/05072

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0612512 A		NZ 219222 A SU 1828400 A TR 23643 A	27-10-1989 15-07-1993 28-05-1990